Secondary structure of a Bim peptide is stabilized by anchoring its N-terminus

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The interaction of an α-helical domain of one protein with a shallow groove of another is found in a lot of proteins.[1] As an example, there is the interaction between Bim and Bax proteins involved in apoptosis. This interaction also adopts to a fragment peptide in the Bim protein (Bim peptide).
So far, We have attained effective apoptosis induction inside cells using the Bim peptide. Furthermore, we have investigated the effect of truncation of the Bim peptide on its apoptosis induction.[2]

However, truncation of the Bim peptide will induces destabilization of the secondary structure (α-helix) of the peptide. We are concerned that this destabilization leads to decreased expression of apoptosis induction. Therefore, in the present study, we designed an N-terminally stapled Bim peptide to stabilize the secondary structure of the truncated Bim peptide.

When a peptide forms an α-helix structure, its terminal four amides have no hydrogen-bonding partners.[3] This is expected to cause destabilization of the α-helical structure. In this design, stapling one of their ends is expected to improve the stability of the secondary structure. Furthermore, this stapling promotes the nucleation of the peptide at the end, which is expected to further stabilize the secondary structure of the entire peptide.
Figure 1 shows the synthesis of the peptide. Peptide **1** was synthesized by Fmoc solid-phase peptide synthesis. After deprotection of Fmoc group of the elongated peptide on a resin, DMF solution of activated bromoacetic acid was added to the resin and stirred for 3 h to obtain **2**. The resin was washed before S-trityl-2-mercaptoethylamine and DIEA were dissolved in DMF, then added to the resin, and stirred for 3 h to obtain **3**. The resin was mixed with Fmoc-Ile-OH with the coupling reagents at 60°C for 45 min. After deprotection and washing, **4** was obtained on the resin. Fmoc-Trp(Boc)-OH was then coupled, deprotected and washed. Then (tritylthio)acetic acid and the coupling reagents were added and stirred for 3 h. After washing with DCM, the peptides were dried and cleavaged from the resin to obtain **5**. After purification, **5** was dissolved in 50% water and 50% DMSO and stirred for 1 day to obtain **6**.

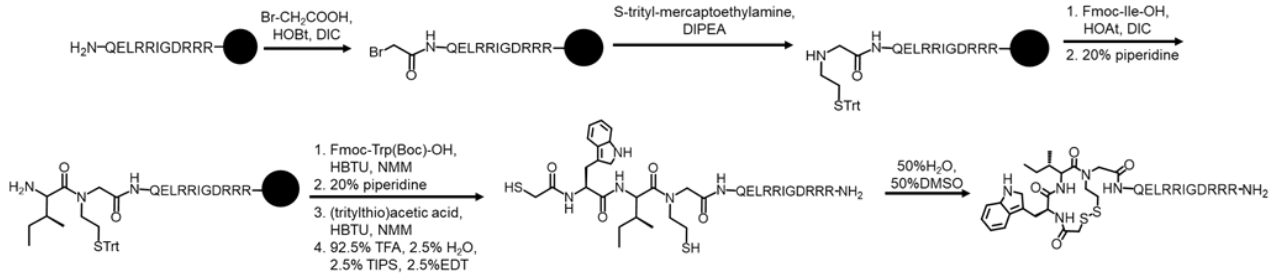

Figure 1. Synthetic route of the stapled Bim peptide 6.

References

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